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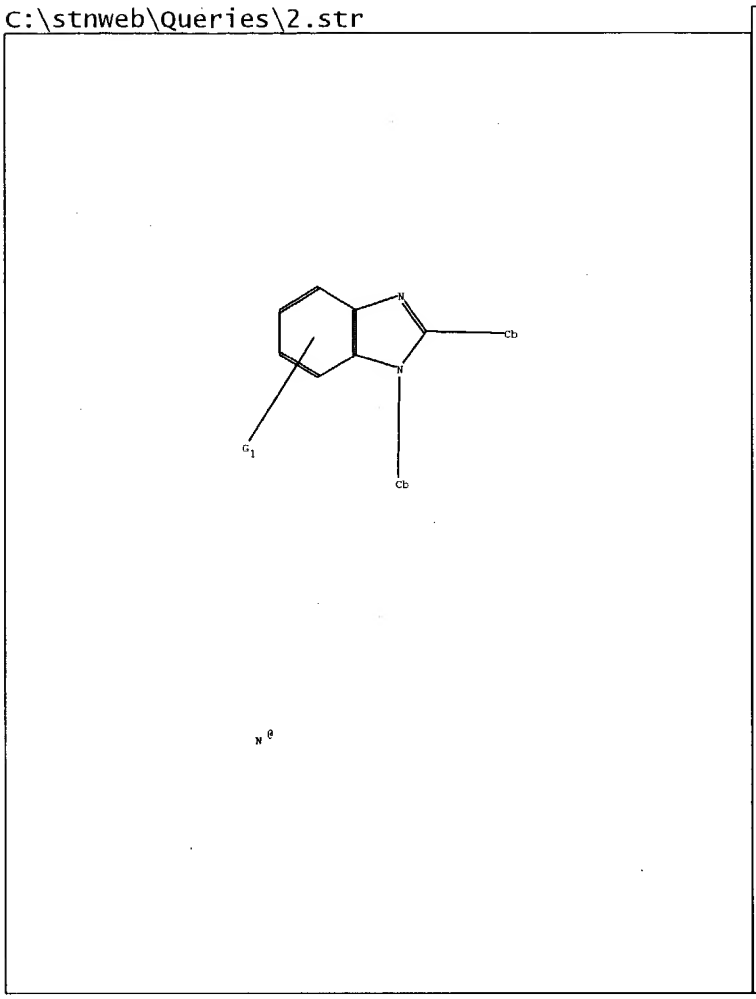

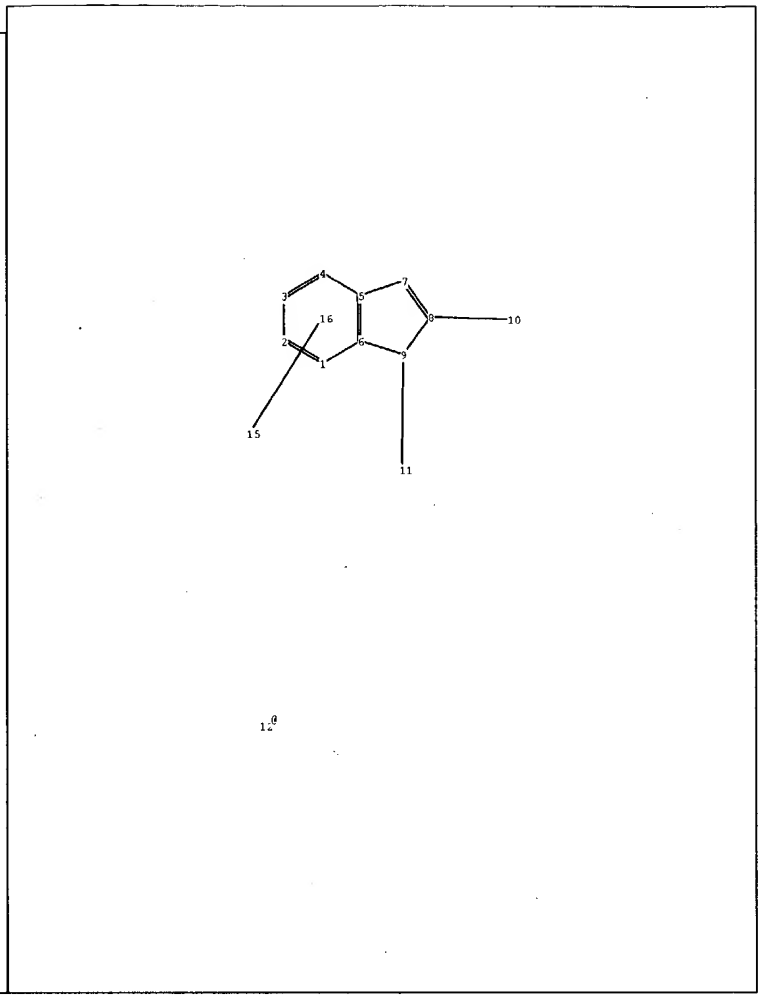

chain nodes :
10 11 12 15
ring nodes :
1 2 3 4 5 6 7 8 9
chain bonds :
8-10 9-11
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-9 7-8 8-9
exact/norm bonds :
5-7 6-9 7-8 8-9
exact bonds :
8-10 9-11
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6
isolated ring systems :
containing 1 :

G1:O,S,SO2,NH

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
12:CLASS 15:CLASS 16:CLASS

```
* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

NEWS   1           Web Page URLs for STN Seminar Schedule - N. America
NEWS   2           "Ask CAS" for self-help around the clock
NEWS   3  Jul 12   BEILSTEIN enhanced with new display and select options,
                   resulting in a closer connection to BABS
NEWS   4  Jul 30   BEILSTEIN on STN workshop to be held August 24 in conjunction
                   with the 228th ACS National Meeting
NEWS   5  AUG 02   IFIPAT/IFIUDB/IFICDB reloaded with new search and display
                   fields
NEWS   6  AUG 02   CAplus and CA patent records enhanced with European and Japan
                   Patent Office Classifications
NEWS   7  AUG 02   The Analysis Edition of STN Express with Discover!
                   (Version 7.01 for Windows) now available
NEWS   8  AUG 04   Pricing for the Save Answers for SciFinder Wizard within
                   STN Express with Discover! will change September 1, 2004
NEWS   9  AUG 27   BIOCOMMERCE: Changes and enhancements to content coverage
NEWS  10  AUG 27   BIOTECHABS/BIOTECHDS: Two new display fields added for legal
                   status data from INPADOC
NEWS  11  SEP 01   INPADOC: New family current-awareness alert (SDI) available
NEWS  12  SEP 01   New pricing for the Save Answers for SciFinder Wizard within
                   STN Express with Discover!
NEWS  13  SEP 01   New display format, HITSTR, available in WPIDS/WPINDEX/WPIX
NEWS  14  SEP 14   STN Patent Forum to be held October 13, 2004, in Iselin, NJ

NEWS EXPRESS  JULY 30 CURRENT WINDOWS VERSION IS V7.01, CURRENT
              MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
              AND CURRENT DISCOVER FILE IS DATED 11 AUGUST 2004
NEWS HOURS    STN Operating Hours Plus Help Desk Availability
NEWS INTER    General Internet Information
NEWS LOGIN    Welcome Banner and News Items
NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
NEWS WWW      CAS World Wide Web Site (general information)

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=> file reg
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 0.21       0.21

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provided by InfoChem.
```

h eb c g cg b cg eb

STRUCTURE FILE UPDATES: 22 SEP 2004 HIGHEST RN 749824-02-0
DICTIONARY FILE UPDATES: 22 SEP 2004 HIGHEST RN 749824-02-0

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

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Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
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L1 STRUCTURE UPLOADED

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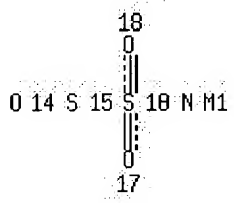
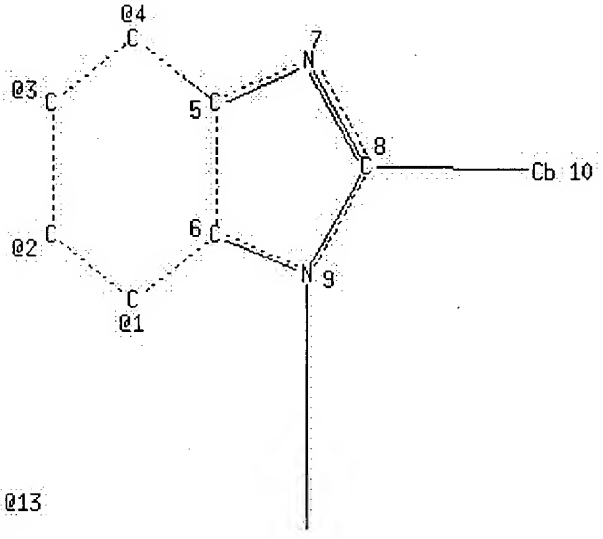
L1 HAS NO ANSWERS
L1 STR



Page 1-A



G1 @13

Page 1-B

Cb 11
Page 2-B
N 12
Page 3-B
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VPA 13-1/2/3/4 S
NODE ATTRIBUTES:
HCOUNT IS M1 AT 19

h eb c g cg b cg eb

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NSPEC   IS R      AT   2
NSPEC   IS R      AT   3
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NSPEC   IS R      AT   6
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NSPEC   IS C      AT  12
NSPEC   IS C      AT  13
DEFAULT MLEVEL IS ATOM
MLEVEL  IS CLASS  AT  12 14 15 16 17 18 19
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS  19

STEREO ATTRIBUTES: NONE


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SAMPLE SEARCH INITIATED 11:18:00 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -  15927 TO ITERATE

  6.3% PROCESSED    1000 ITERATIONS                          1 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       310985 TO   326095
PROJECTED ANSWERS:              79 TO      557

L2            1 SEA SSS SAM L1

=> s l1 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 11:18:04 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 317761 TO ITERATE

100.0% PROCESSED  317761 ITERATIONS                      171 ANSWERS
SEARCH TIME: 00.00.07

L3          171 SEA SSS FUL L1

=> file hcaplus
COST IN U.S. DOLLARS                        SINCE FILE      TOTAL
                                               ENTRY    SESSION
FULL ESTIMATED COST                           158.78     158.99

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h eb c g cg b cg eb

FILE COVERS 1907 - 24 Sep 2004 VOL 141 ISS 14
FILE LAST UPDATED: 23 Sep 2004 (20040923/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> s l3/thu
            20 L3
        621837 THU/RL
L4          13 L3/THU
                (L3 (L) THU/RL)

=> s l4 and inflammation?
        110337 INFLAMMATION?
L5           3 L4 AND INFLAMMATION?

=> s l5 and halfbrodt, w?/au
            20 HALFBRODT, W?/AU
L6           1 L5 AND HALFBRODT, W?/AU

=> d l6, ibib abs fhitstr, 1

L6   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

ACCESSION NUMBER: 2003:42104 HCAPLUS
DOCUMENT NUMBER: 138:106697
TITLE: Preparation of 1-alkyl-2-arylbenzimidazole derivatives for treatment of diseases linked to the activation of microglia
INVENTOR(S): Blume, Thorsten; **Halfbrodt, Wolfgang**; Kuhnke, Joachim; Moenning, Ursula; Elger, Bernd; Schneider, Herbert
PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003004023	A1	20030116	WO 2002-EP7597	20020706

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,

h eb c g cg b cg eb

PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG

DE 10134775	A1	20030130	DE 2001-10134775	20010706
US 2003055057	A1	20030320	US 2002-189179	20020705
EP 1404321	A1	20040407	EP 2002-762333	20020706

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, BG, CZ, EE, SK

PRIORITY APPLN. INFO.:	DE 2001-10134775	A	20010706
	US 2002-347242P	P	20020114
	WO 2002-EP7597	W	20020706

OTHER SOURCE(S): MARPAT 138:106697
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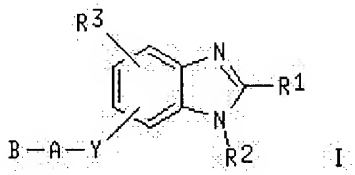

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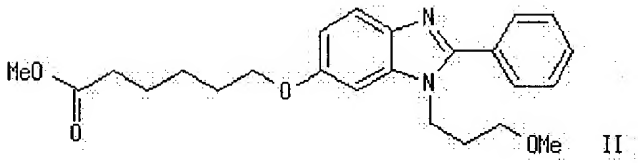

II

AB Title compds. I [wherein R1 = (un)substituted (hetero)aryl, esp. benzothienyl or indolyl; R2 = (un)substituted (cyclo)alkyl, alkenyl, hydroxyalkyl, aminoalkyl, carbamoylalkyl, Ph, etc.; R3 = H, F, Cl, Br, OH, CN, NO2, or (un)substituted carbamoyl(oxy), sulfamoyl, amino, ureido, etc.; A = (un)substituted alkanediyl, alkenediyl, or alkynediyl, cycloalkyl ring, heterocyclyl ring, etc.; B = CO2H, carboxy ester, carbamoyl, etc.; Y = O, NH, (un)substituted ureido, sulfamoyl, etc.] were prepd. as microglia activation inhibitors. For example, a multi-step synthesis starting from 3-fluoro-4-nitrophenol, 3-methoxypropylamine, Me 6-bromohexanoate, and tri-Me orthobenzoate produced 6-[[5-(methoxycarbonyl)pentyl]oxy]-1-(3-methoxypropyl)-2-phenylbenzimidazole (II). The latter inhibited Aβ-activation of microglia in vitro with an IC50 of 0.65 μM. Thus, I are useful for the prophylaxis and treatment of diseases linked to the activation of microglia, such as **inflammation**, allergy, infection, autoimmune disease, and stroke (no data).

IT **486417-63-4P**, 1-Cyclohexyl-6-[[5-[(3-methylbutyl)aminocarbonyl]pentyl]oxy]-2-phenylbenzimidazole
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(microglia activation inhibitor; prepn. of (alkyl)(aryl)benzimidazoles as microglia activation inhibitors for treatment of **inflammation**, allergy, infection, autoimmune disease, and stroke)

RN 486417-63-4 HCAPLUS
CN Hexanamide, 6-[(1-cyclohexyl-2-phenyl-1H-benzimidazol-6-yl)oxy]-N-(3-methylbutyl)- (9CI) (CA INDEX NAME)

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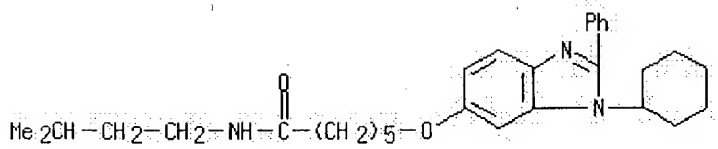

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> d his

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     FILE 'REGISTRY' ENTERED AT 11:12:35 ON 24 SEP 2004
L1             STRUCTURE UPLOADED
L2               1 S L1
L3             171 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 11:18:16 ON 24 SEP 2004
L4              13 S L3/THU
L5               3 S L4 AND INFLAMMATION?
L6               1 S L5 AND HALFBRODT, W?/AU

=> s l5 not l6
L7               2 L5 NOT L6

=> s l7 and kuhnke, j?/au
              27 KUHNKE, J?/AU
L8               0 L7 AND KUHNKE, J?/AU

=> s l7 and moenning, u?/au
              25 MOENNING, U?/AU
L9               0 L7 AND MOENNING, U?/AU

=> d l7, ibib abs fhitstr, 1-2

L7   ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Other References

```
ACCESSION NUMBER:          2003:737580  HCAPLUS
DOCUMENT NUMBER:           139:261298
TITLE:                     Preparation of imidazole and benzimidazole derivatives
                           that inhibit the interaction of ligands with RAGE
INVENTOR(S):               Mjalli, Adnan M. M.; Andrews, Robert C.; Gopalaswamy,
                           Ramesh; Hari, Anitha; Avor, Kwasi; Qabaja, Ghassan;
                           Guo, Xiao-Chuan; Gupta, Suparna; Jones, David R.;
                           Chen, Xin
PATENT ASSIGNEE(S):        Transtech Pharma, Inc., USA
SOURCE:                    PCT Int. Appl., 462 pp.
                           CODEN: PIXXD2
DOCUMENT TYPE:             Patent
LANGUAGE:                  English
FAMILY ACC. NUM. COUNT:    1
PATENT INFORMATION:
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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003075921	A2	20030918	WO 2003-US6749	20030305

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WO 2003075921 A3 20031204
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2004082542 A1 20040429 US 2003-382203 20030305
PRIORITY APPLN. INFO.: US 2002-361983P P 20020305
OTHER SOURCE(S): MARPAT 139:261298
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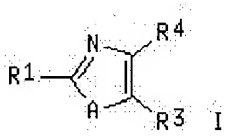

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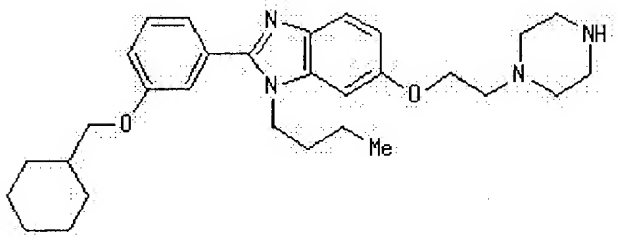

II

AB Title compds. and analogs I [wherein A = O, S, or NR2; R1 and R2 = independently H or (un)substituted (hetero)aryl, (cyclo)alkyl, heterocyclyl, alkenyl, alkynyl, alkylene(hetero)aryl, alkylene heterocyclyl, alkylene cycloalkyl, etc.; R3 and R4 = independently H, halo, OH, CN, CONH2, CO2H, or (un)substituted (hetero)aryl, (cyclo)alkyl, heterocyclyl, alkenyl, alkynyl, alkylene(hetero)aryl, alkylene heterocyclyl, alkylene cycloalkyl, etc.; and pharmaceutically acceptable salts thereof] were prepd. as modulators of the interaction between the receptor for advanced glycated end products (RAGE) and its ligands, such as advanced glycated end products (AGEs), S100/calgranulin/EN-RAGE, β-amyloid, and amphoterin. For example, 1-BOC-4-[2-(4-amino-3-butylaminophenoxy)ethyl]piperazine was condensed with 3-hydroxybenzaldehyde to give the hydroxybenzimidazole. Coupling with cyclohexylmethyl bromide in the presence of NaH in THF afforded II. In binding studies employing S100b as the RAGE ligand, five hundred fifty-one invention compds. exhibited binding with IC50 values of < 10 μM. Thus, I and their pharmaceutical compns. are useful for the management, treatment, control, or as an adjunct treatment for diseases in humans caused by RAGE, including acute and chronic **inflammation**, the development of diabetic late complications such as increased vascular permeability, nephropathy, atherosclerosis, and retinopathy, the development of Alzheimer's disease, erectile dysfunction, and tumor invasion and metastasis (no data).
IT **603145-50-2P**, N-[3-[[2-[4-(Benzyloxy)phenyl]-3-cyclopentyl-3H-benzimidazol-5-yl]oxy]propyl]-N,N-diethylamine

h eb c g cg b cg eb

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      1760403 REVIEW/DT
L16           0 L13 AND REVIEW/DT

=> s l12 and review/dt
      1760403 REVIEW/DT
L17          23 L12 AND REVIEW/DT

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           1778 INFLAMMATIONS
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         471082 INHIBITORS
         727119 INHIBITOR
                (INHIBITOR OR INHIBITORS)
L19           2 L18 AND INHIBITOR

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L19  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2004 ACS on STN
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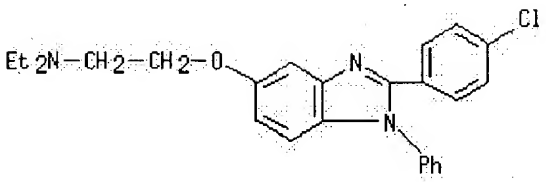
Full Text | Citing References

ACCESSION NUMBER: 2004:197795 HCAPLUS
DOCUMENT NUMBER: 140:314258
TITLE: Minocycline: neuroprotective mechanisms in Parkinson's disease
AUTHOR(S): Thomas, M.; Le, W. D.
CORPORATE SOURCE: Department of Neurology, Baylor College of Medicine, Houston, TX, 77030, USA
SOURCE: Current Pharmaceutical Design (2004), 10(6), 679-686
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Parkinson's disease (PD) is a common neurodegenerative disorder characterized by cardinal features of tremor, bradykinesia, rigidity and postural instability. In addn. to the motor symptoms patients experience cognitive decline eventually resulting in severe disability. Pathol. PD is characterized by neurodegeneration in the substantia nigra pars compacta (SNc) with intracytoplasmic inclusions known as Lewy bodies. In addn. to the SNc there is neurodegeneration in other areas including cerebral cortex, raphe nuclei, locus ceruleus, nucleus basalis of meynert, cranial nerves and autonomic nervous system. Recent evidence supports the role of **inflammation** in Parkinson's disease. Apoptosis has been shown to be one of the pathways of cell death in PD. Minocycline, a tetracycline, a tetracycline deriv. is a caspase **inhibitor**, and also inhibits the inducible nitric oxide synthase which are important for apoptotic cell death. Furthermore, Minocycline has been shown to block **microglial activation** of 6-hydroxydopamine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned parkinsonism animal models and protect against nigrostriatal dopaminergic neurodegeneration. In this review, we present the current exptl. evidence for the potential use of tetracycline deriv., minocycline, as a neuroprotective agent in PD.

REFERENCE COUNT: 96 THERE ARE 96 CITED REFERENCES AVAILABLE FOR THIS



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> file caold

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	21.36	180.35

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-2.10	-2.10

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FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REGlstRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

=> dh is
DH IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter "HELP COMMANDS" at an arrow prompt (=>).

=> d his

(FILE 'HOME' ENTERED AT 11:12:28 ON 24 SEP 2004)

FILE 'REGISTRY' ENTERED AT 11:12:35 ON 24 SEP 2004
L1 STRUCTURE UPLOADED
L2 1 S L1
L3 171 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 11:18:16 ON 24 SEP 2004
L4 13 S L3/THU
L5 3 S L4 AND INFLAMMATION?
L6 1 S L5 AND HALFBRODT, W?/AU
L7 2 S L5 NOT L6
L8 0 S L7 AND KUHNKE, J?/AU
L9 0 S L7 AND MOENNING, U?/AU

h eb c g cg b cg eb

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     FILE 'CAOLD' ENTERED AT 11:20:19 ON 24 SEP 2004

=> s l3
L10             0 L3

=>
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h eb c g cg b cg eb

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                   resulting in a closer connection to BABS
NEWS   4  Jul 30   BEILSTEIN on STN workshop to be held August 24 in conjunction
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NEWS   5  AUG 02   IFIPAT/IFIUDB/IFICDB reloaded with new search and display
                   fields
NEWS   6  AUG 02   CAplus and CA patent records enhanced with European and Japan
                   Patent Office Classifications
NEWS   7  AUG 02   The Analysis Edition of STN Express with Discover!
                   (Version 7.01 for Windows) now available
NEWS   8  AUG 04   Pricing for the Save Answers for SciFinder Wizard within
                   STN Express with Discover! will change September 1, 2004
NEWS   9  AUG 27   BIOCOMMERCE: Changes and enhancements to content coverage
NEWS  10  AUG 27   BIOTECHABS/BIOTECHDS: Two new display fields added for legal
                   status data from INPADOC
NEWS  11  SEP 01   INPADOC: New family current-awareness alert (SDI) available
NEWS  12  SEP 01   New pricing for the Save Answers for SciFinder Wizard within
                   STN Express with Discover!
NEWS  13  SEP 01   New display format, HITSTR, available in WPIDS/WPINDEX/WPIX
NEWS  14  SEP 14   STN Patent Forum to be held October 13, 2004, in Iselin, NJ

NEWS EXPRESS  JULY 30 CURRENT WINDOWS VERSION IS V7.01, CURRENT
              MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
              AND CURRENT DISCOVER FILE IS DATED 11 AUGUST 2004
NEWS HOURS    STN Operating Hours Plus Help Desk Availability
NEWS INTER    General Internet Information
NEWS LOGIN    Welcome Banner and News Items
NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

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FILE 'HOME' ENTERED AT 11:12:28 ON 24 SEP 2004

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'REGISTRY' ENTERED AT 11:12:35 ON 24 SEP 2004
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provided by InfoChem.
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STRUCTURE FILE UPDATES: 22 SEP 2004 HIGHEST RN 749824-02-0
DICTIONARY FILE UPDATES: 22 SEP 2004 HIGHEST RN 749824-02-0

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

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Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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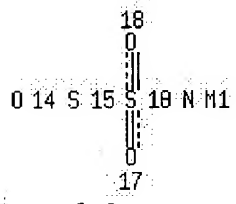
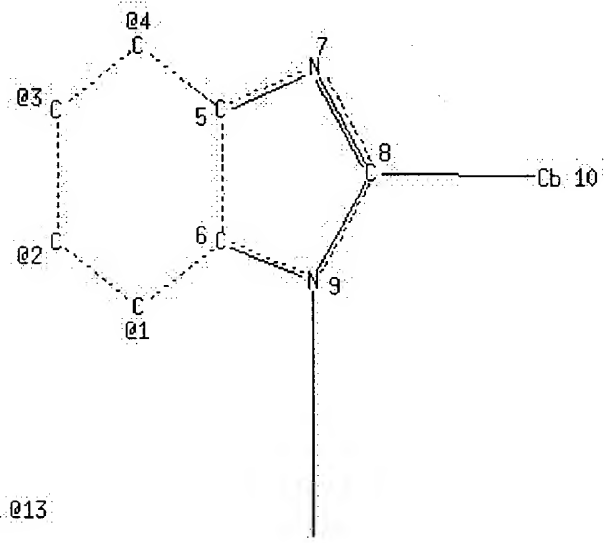


Page 1-A



G1 @13

Page 1-B

Cb 11

Page 2-B

N 12

Page 3-B

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HCOUNT IS M1 AT 19

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS  19

STEREO ATTRIBUTES: NONE


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SAMPLE SCREEN SEARCH COMPLETED -  15927 TO ITERATE

  6.3% PROCESSED    1000 ITERATIONS                              1 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       310985 TO   326095
PROJECTED ANSWERS:              79 TO      557

L2            1 SEA SSS SAM L1

=> s l1 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 11:18:04 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 317761 TO ITERATE

100.0% PROCESSED  317761 ITERATIONS                            171 ANSWERS
SEARCH TIME: 00.00.07

L3          171 SEA SSS FUL L1

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COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                             158.78     158.99

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h eb c g cg b cg eb

FILE COVERS 1907 - 24 Sep 2004 VOL 141 ISS 14
FILE LAST UPDATED: 23 Sep 2004 (20040923/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

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            20 L3
        621837 THU/RL
L4          13 L3/THU
                (L3 (L) THU/RL)

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        110337 INFLAMMATION?
L5           3 L4 AND INFLAMMATION?

=> s l5 and halfbrodt, w?/au
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L6           1 L5 AND HALFBRODT, W?/AU

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L6   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

ACCESSION NUMBER: 2003:42104 HCAPLUS
DOCUMENT NUMBER: 138:106697
TITLE: Preparation of 1-alkyl-2-arylbenzimidazole derivatives for treatment of diseases linked to the activation of microglia
INVENTOR(S): Blume, Thorsten; **Halfbrodt, Wolfgang**; Kuhnke, Joachim; Moenning, Ursula; Elger, Bernd; Schneider, Herbert
PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003004023	A1	20030116	WO 2002-EP7597	20020706

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h eb c g cg b cg eb

PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG

DE 10134775	A1	20030130	DE 2001-10134775	20010706
US 2003055057	A1	20030320	US 2002-189179	20020705
EP 1404321	A1	20040407	EP 2002-762333	20020706

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, BG, CZ, EE, SK

PRIORITY APPLN. INFO.:	DE 2001-10134775	A	20010706
	US 2002-347242P	P	20020114
	WO 2002-EP7597	W	20020706

OTHER SOURCE(S): MARPAT 138:106697

GI

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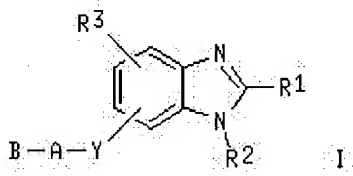

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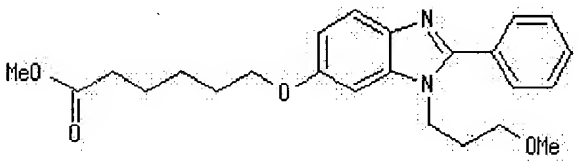

II

AB Title compds. I [wherein R1 = (un)substituted (hetero)aryl, esp. benzothienyl or indolyl; R2 = (un)substituted (cyclo)alkyl, alkenyl, hydroxyalkyl, aminoalkyl, carbamoylalkyl, Ph, etc.; R3 = H, F, Cl, Br, OH, CN, NO2, or (un)substituted carbamoyl(oxy), sulfamoyl, amino, ureido, etc.; A = (un)substituted alkanediyl, alkenediyl, or alkynediyl, cycloalkyl ring, heterocyclyl ring, etc.; B = CO2H, carboxy ester, carbamoyl, etc.; Y = O, NH, (un)substituted ureido, sulfamoyl, etc.] were prepd. as microglia activation inhibitors. For example, a multi-step synthesis starting from 3-fluoro-4-nitrophenol, 3-methoxypropylamine, Me 6-bromohexanoate, and tri-Me orthobenzoate produced 6-[[5-(methoxycarbonyl)pentyl]oxy]-1-(3-methoxypropyl)-2-phenylbenzimidazole (II). The latter inhibited Aβ-activation of microglia in vitro with an IC50 of 0.65 μM. Thus, I are useful for the prophylaxis and treatment of diseases linked to the activation of microglia, such as **inflammation**, allergy, infection, autoimmune disease, and stroke (no data).

IT **486417-63-4P**, 1-Cyclohexyl-6-[[5-[(3-methylbutyl)aminocarbonyl]pentyl]oxy]-2-phenylbenzimidazole
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(microglia activation inhibitor; prepn. of (alkyl)(aryl)benzimidazoles as microglia activation inhibitors for treatment of **inflammation**, allergy, infection, autoimmune disease, and stroke)

RN 486417-63-4 HCAPLUS

CN Hexanamide, 6-[(1-cyclohexyl-2-phenyl-1H-benzimidazol-6-yl)oxy]-N-(3-methylbutyl)- (9CI) (CA INDEX NAME)

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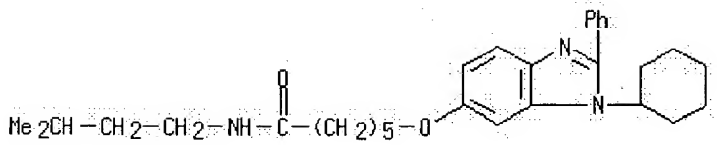

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FILE 'REGISTRY' ENTERED AT 11:12:35 ON 24 SEP 2004
L1 STRUCTURE UPLOADED
L2 1 S L1
L3 171 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 11:18:16 ON 24 SEP 2004
L4 13 S L3/THU
L5 3 S L4 AND INFLAMMATION?
L6 1 S L5 AND HALFBRODT, W?/AU

=> s l5 not l6
L7 2 L5 NOT L6

=> s l7 and kuhnke, j?/au
27 KUHNKE, J?/AU
L8 0 L7 AND KUHNKE, J?/AU

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25 MOENNING, U?/AU
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L7 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Other References

ACCESSION NUMBER: 2003:737580 HCAPLUS
DOCUMENT NUMBER: 139:261298
TITLE: Preparation of imidazole and benzimidazole derivatives that inhibit the interaction of ligands with RAGE
INVENTOR(S): Mjalli, Adnan M. M.; Andrews, Robert C.; Gopalaswamy, Ramesh; Hari, Anitha; Avor, Kwasi; Qabaja, Ghassan; Guo, Xiao-Chuan; Gupta, Suparna; Jones, David R.; Chen, Xin
PATENT ASSIGNEE(S): Transtech Pharma, Inc., USA
SOURCE: PCT Int. Appl., 462 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003075921	A2	20030918	WO 2003-US6749	20030305

h eb c g cg b cg eb

WO 2003075921 A3 20031204
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2004082542 A1 20040429 US 2003-382203 20030305
PRIORITY APPLN. INFO.: US 2002-361983P P 20020305
OTHER SOURCE(S): MARPAT 139:261298
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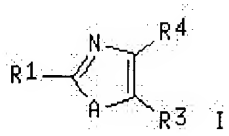

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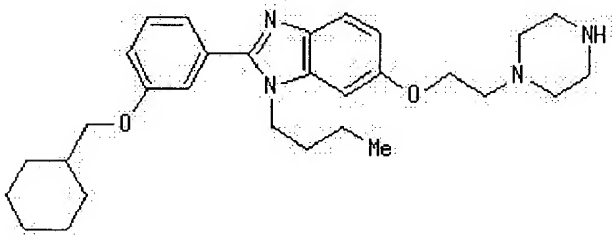


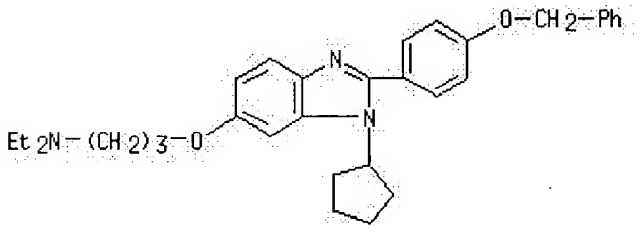
II

AB Title compds. and analogs I [wherein A = O, S, or NR2; R1 and R2 = independently H or (un)substituted (hetero)aryl, (cyclo)alkyl, heterocyclyl, alkenyl, alkynyl, alkylene(hetero)aryl, alkylene heterocyclyl, alkylene cycloalkyl, etc.; R3 and R4 = independently H, halo, OH, CN, CONH2, CO2H, or (un)substituted (hetero)aryl, (cyclo)alkyl, heterocyclyl, alkenyl, alkynyl, alkylene(hetero)aryl, alkylene heterocyclyl, alkylene cycloalkyl, etc.; and pharmaceutically acceptable salts thereof] were prepd. as modulators of the interaction between the receptor for advanced glycated end products (RAGE) and its ligands, such as advanced glycated end products (AGEs), S100/calgranulin/EN-RAGE, β-amyloid, and amphoterin. For example, 1-BOC-4-[2-(4-amino-3-butylaminophenoxy)ethyl]piperazine was condensed with 3-hydroxybenzaldehyde to give the hydroxybenzimidazole. Coupling with cyclohexylmethyl bromide in the presence of NaH in THF afforded II. In binding studies employing S100b as the RAGE ligand, five hundred fifty-one invention compds. exhibited binding with IC50 values of < 10 μM. Thus, I and their pharmaceutical compns. are useful for the management, treatment, control, or as an adjunct treatment for diseases in humans caused by RAGE, including acute and chronic **inflammation**, the development of diabetic late complications such as increased vascular permeability, nephropathy, atherosclerosis, and retinopathy, the development of Alzheimer's disease, erectile dysfunction, and tumor invasion and metastasis (no data).
IT **603145-50-2P**, N-[3-[[2-[4-(Benzyloxy)phenyl]-3-cyclopentyl-3H-benzimidazol-5-yl]oxy]propyl]-N,N-diethylamine

h eb c g cg b cg eb

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(RAGE modulator; prepn. of imidazole and benzimidazole RAGE modulators for treatment of **inflammation**, diabetes, tumors, and other conditions)

RN 603145-50-2 HCAPLUS
CN 1-Propanamine, 3-[[1-cyclopentyl-2-[4-(phenylmethoxy)phenyl]-1H-benzimidazol-6-yl]oxy]-N,N-diethyl- (9CI) (CA INDEX NAME)



L7 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

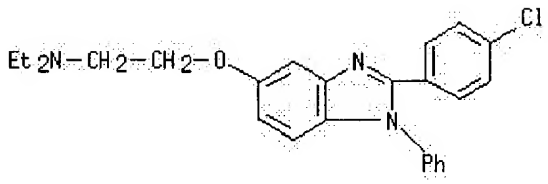
Full Text | Chem References

ACCESSION NUMBER: 2000:297304 HCAPLUS
DOCUMENT NUMBER: 133:202600
TITLE: A quantitative structure-activity relationship analysis of some substituted oxazolopyridines and benzimidazoles with antiinflammatory activity
AUTHOR(S): Chakravarti, S. K.; Chaturvedi, S. C.
CORPORATE SOURCE: Department of Pharmacy, Shri Govindram Seksaria Institute of Technology and Science, Indore, 452003, India
SOURCE: Indian Journal of Pharmaceutical Sciences (1999), 61(4), 206-212
CODEN: IJSIDW; ISSN: 0250-474X
PUBLISHER: Indian Pharmaceutical Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The lowest energy conformations of some antiinflammatory 2-(substituted phenyl)oxazolopyridines, 2-(substituted pyridinyl) benzimidazoles and 1H-benzimidazoles were calcd. and quant. structure-activity relationship anal. was then performed on each category of compds. using thermodn., electronic and spatial descriptors. The resulting QSAR equations were validated by leave-one-out cross validation method. Electronic parameter (dipole moment) and spatial parameters (mol. vol. and principal moment of inertia) were found to have significant correlation with antiinflammatory activity.

IT **289893-74-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(QSAR of substituted oxazolopyridines and benzimidazoles with antiinflammatory activity)

RN 289893-74-9 HCAPLUS
CN Ethanamine, 2-[[2-(4-chlorophenyl)-1-phenyl-1H-benzimidazol-5-yl]oxy]-N,N-diethyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FULL ESTIMATED COST	21.36	180.35

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-2.10	-2.10

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FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REGlstRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

=> dh is
DH IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d his

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FILE 'REGISTRY' ENTERED AT 11:12:35 ON 24 SEP 2004
L1 STRUCTURE UPLOADED
L2 1 S L1
L3 171 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 11:18:16 ON 24 SEP 2004
L4 13 S L3/THU
L5 3 S L4 AND INFLAMMATION?
L6 1 S L5 AND HALFBRODT, W?/AU
L7 2 S L5 NOT L6
L8 0 S L7 AND KUHNKE, J?/AU
L9 0 S L7 AND MOENNING, U?/AU

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L10             0 L3

=> file hcaplus
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FULL ESTIMATED COST                                     0.42     180.77

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CA SUBSCRIBER PRICE                                     0.00      -2.10

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FILE COVERS 1907 - 24 Sep 2004  VOL 141 ISS 14
FILE LAST UPDATED: 23 Sep 2004  (20040923/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


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        689658 ACTIVATION?
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=> s l11 and inflammation?
        110337 INFLAMMATION?
L12        169 L11 AND INFLAMMATION?

=> s microglia? () activation? () inhibitor?
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        894936 INHIBITOR?
L13          2 MICROGLIA? (W) ACTIVATION? (W) INHIBITOR?

=> s l13 and inflammation?
        110337 INFLAMMATION?
L14          1 L13 AND INFLAMMATION?

=> s l14 and review/dt
       1760403 REVIEW/DT
L15          0 L14 AND REVIEW/DT
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h ebc gcgb cg eb

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L14  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2004 ACS on STN
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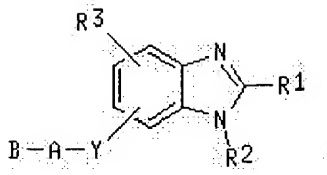
Full Text | CAPLUS References

ACCESSION NUMBER: 2003:42104 HCAPLUS
DOCUMENT NUMBER: 138:106697
TITLE: Preparation of 1-alkyl-2-arylbenzimidazole derivatives for treatment of diseases linked to the activation of microglia
INVENTOR(S): Blume, Thorsten; Halfbrodt, Wolfgang; Kuhnke, Joachim; Moenning, Ursula; Elger, Bernd; Schneider, Herbert
PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003004023	A1	20030116	WO 2002-EP7597	20020706
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10134775	A1	20030130	DE 2001-10134775	20010706
US 2003055057	A1	20030320	US 2002-189179	20020705
EP 1404321	A1	20040407	EP 2002-762333	20020706
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, BG, CZ, EE, SK				

PRIORITY APPLN. INFO.:			
	DE 2001-10134775	A	20010706
	US 2002-347242P	P	20020114
	WO 2002-EP7597	W	20020706

OTHER SOURCE(S): MARPAT 138:106697
GI



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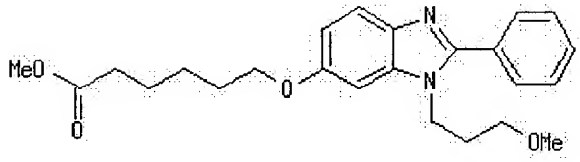

II

AB Title compds. I [wherein R1 = (un)substituted (hetero)aryl, esp. benzothienyl or indolyl; R2 = (un)substituted (cyclo)alkyl, alkenyl, hydroxyalkyl, aminoalkyl, carbamoylalkyl, Ph, etc.; R3 = H, F, Cl, Br, OH, CN, NO2, or (un)substituted carbamoyl(oxy), sulfamoyl, amino, ureido, etc.; A = (un)substituted alkanediyl, alkenediyl, or alkynediyl, cycloalkyl ring, heterocyclyl ring, etc.; B = CO2H, carboxy ester, carbamoyl, etc.; Y = O, NH, (un)substituted ureido, sulfamoyl, etc.] were prepd. as **microglia activation inhibitors**. For example, a multi-step synthesis starting from 3-fluoro-4-nitrophenol, 3-methoxypropylamine, Me 6-bromohexanoate, and tri-Me orthobenzoate produced 6-[[5-(methoxycarbonyl)pentyl]oxy]-1-(3-methoxypropyl)-2-phenylbenzimidazole (II). The latter inhibited Aβ-activation of microglia in vitro with an IC50 of 0.65 μM. Thus, I are useful for the prophylaxis and treatment of diseases linked to the activation of microglia, such as **inflammation**, allergy, infection, autoimmune disease, and stroke (no data).

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 11:12:28 ON 24 SEP 2004)

FILE 'REGISTRY' ENTERED AT 11:12:35 ON 24 SEP 2004
L1 STRUCTURE UPLOADED
L2 1 S L1
L3 171 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 11:18:16 ON 24 SEP 2004
L4 13 S L3/THU
L5 3 S L4 AND INFLAMMATION?
L6 1 S L5 AND HALFBRODT, W?/AU
L7 2 S L5 NOT L6
L8 0 S L7 AND KUHNKE, J?/AU
L9 0 S L7 AND MOENNING, U?/AU

FILE 'CAOLD' ENTERED AT 11:20:19 ON 24 SEP 2004
L10 0 S L3

FILE 'HCAPLUS' ENTERED AT 11:20:42 ON 24 SEP 2004
L11 714 S MICROGLIA? () ACTIVATION?
L12 169 S L11 AND INFLAMMATION?
L13 2 S MICROGLIA? () ACTIVATION? () INHIBITOR?
L14 1 S L13 AND INFLAMMATION?
L15 0 S L14 AND REVIEW/DT

h eb c g cg b cg eb

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2004:153999 HCAPLUS
DOCUMENT NUMBER: 141:51457
TITLE: Rat models of dementia based on reductions in regional glucose metabolism, cerebral blood flow and cytochrome oxidase activity
AUTHOR(S): Weinstock, M.; Shoham, S.
CORPORATE SOURCE: School of Pharmacy, Department of Pharmacology, Hebrew University Medical Centre, Jerusalem, 91120, Israel
SOURCE: Journal of Neural Transmission (2004), 111(3), 347-366
CODEN: JNTRF3; ISSN: 0300-9564
PUBLISHER: Springer-Verlag Wien
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Three models are described in rats which attempt to mimic morphol. and behavioral pathol. of Alzheimer's dementia; intracerebroventricular injection of streptozotocin (STZ), permanent bilateral carotid artery occlusion (2VO) and brain mitochondrial cytochrome oxidase inhibition by sodium azide. Learning and memory are impaired within 4 wk in all models. This probably involves a redn. in cortical and/or hippocampal cholinergic neurotransmission. STZ causes **microglial activation** and specific damage to myelinated tracts in the fornix through generation of oxidative stress, thereby disrupting connections between the septum and hippocampus. 2VO results in damage to myelin and CA1 cells in hippocampus and in abnormal processing of APP to β-amyloid. It is not known if **microglial activation** and neuronal damage occur after sodium azide administration. Memory and learning can be improved in the STZ and 2VO models by estradiol, melatonin and cholinesterase **inhibitors**. Antioxidants and neuroprotective agents may also decrease memory deficits by preventing **inflammation** and neurodegeneration.

REFERENCE COUNT: 94 THERE ARE 94 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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(FILE 'HOME' ENTERED AT 11:12:28 ON 24 SEP 2004)

FILE 'REGISTRY' ENTERED AT 11:12:35 ON 24 SEP 2004
L1 STRUCTURE UPLOADED
L2 1 S L1
L3 171 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 11:18:16 ON 24 SEP 2004
L4 13 S L3/THU
L5 3 S L4 AND INFLAMMATION?
L6 1 S L5 AND HALFBRODT, W?/AU
L7 2 S L5 NOT L6
L8 0 S L7 AND KUHNKE, J?/AU
L9 0 S L7 AND MOENNING, U?/AU

FILE 'CAOLD' ENTERED AT 11:20:19 ON 24 SEP 2004
L10 0 S L3

FILE 'HCAPLUS' ENTERED AT 11:20:42 ON 24 SEP 2004

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L11          714 S MICROGLIA? () ACTIVATION?
L12          169 S L11 AND INFLAMMATION?
L13            2 S MICROGLIA? () ACTIVATION? () INHIBITOR?
L14            1 S L13 AND INFLAMMATION?
L15            0 S L14 AND REVIEW/DT
L16            0 S L13 AND REVIEW/DT
L17           23 S L12 AND REVIEW/DT
L18           23 S L17 AND INFLAMMATION
L19            2 S L18 AND INHIBITOR

=> s l18 not l19
L20          21 L18 NOT L19

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L20  ANSWER 1 OF 21  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

ACCESSION NUMBER: 2004:592261 HCAPLUS
DOCUMENT NUMBER: 141:137417
TITLE: Navigating novel mechanisms of cellular plasticity with the NAD+ precursor and nutrient nicotinamide
AUTHOR(S): Li, Faqi; Chong, Zhao Zhong; Maiese, Kenneth
CORPORATE SOURCE: Division of Cellular and Molecular Cerebral Ischemia, Wayne State University School of Medicine, Detroit, MI, 48201, USA
SOURCE: Frontiers in Bioscience (2004), 9(Suppl.), 2500-2520
CODEN: FRBIF6; ISSN: 1093-4715
URL: http://www.bioscience.org/2004/v9/af/1412/pdf.pdf
PUBLISHER: Frontiers in Bioscience
DOCUMENT TYPE: Journal; **General Review**; (online computer file)
LANGUAGE: English

AB A review. Interest in neuroprotectants for the central nervous system continues to garner significant attention. Nicotinamide, the amide form of niacin (vitamin B3), is the precursor for the coenzyme β-NAD (NAD+) and is considered to be necessary for cellular function and metab. However, recent work has focused on the development of nicotinamide as a novel agent that is crit. for modulating cellular plasticity, longevity, and inflammatory microglial function. The ability of nicotinamide to preserve both neuronal and vascular cell populations in the brain during injury is intriguing, but further knowledge of the specific cellular mechanisms that det. protection by this agent is required. The capacity of nicotinamide to govern not only intrinsic cellular integrity, but also extrinsic cellular **inflammation** rests with the modulation of a host of cellular targets that involve protein kinase β, glycogen synthase kinase-3β (GSK-3β), Forkhead transcription factors, mitochondrial dysfunction, poly(ADP-ribose) polymerase, cysteine proteases, and **microglial activation**. Intimately tied to the cytoprotection of nicotinamide is the modulation of an early and late phase of apoptotic injury that is triggered by the loss of membrane asymmetry. Identifying robust cytoprotective agents as nicotinamide in conjunction with the elucidation of the cellular mechanisms responsible for cell survival will continue to solidify the development of therapeutic strategies against neurodegenerative diseases.

REFERENCE COUNT: 215 THERE ARE 215 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 2 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

h eb c g cg b cg eb

Full Text | Citing References

ACCESSION NUMBER: 2004:445365 HCAPLUS
DOCUMENT NUMBER: 141:222583
TITLE: The microglial phagocytic role with specific plaque types in the Alzheimer disease brain
AUTHOR(S): D'Andrea, Michael R.; Cole, Gregory M.; Ard, March D.
CORPORATE SOURCE: Johnson & Johnson Pharmaceutical Research and Development, Spring House, PA, 19477, USA
SOURCE: Neurobiology of Aging (2004), 25(5), 675-683
CODEN: NEAGDO; ISSN: 0197-4580
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Alzheimer disease (AD) involves glial **inflammation** assocd. with amyloid plaques. The role of the microglial cells in the AD brain is controversial, as it remains unclear if the microglia form the amyloid fibrils of plaques or react to them in a macrophage-phagocytic role. Also, it is not known why microglia are preferentially assocd. with some amyloid plaque types. This review will provide substantial evidence to support the phagocytic role of microglia in the brain as well as explain why microglia are generally assocd. with specific plaque types that may be explained through their unique mechanisms of formation. In summary, these data suggest that plaque assocd. **microglial activation** is typically subsequent to specific amyloid plaque formations in the AD brain.

REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 3 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2004:261374 HCAPLUS
DOCUMENT NUMBER: 141:138631
TITLE: Is repetitive opportunistic infection in AIDS patients the effective mechanism for neurodegeneration in terms of endlessly amplifying cytokine/chemokine effect?
AUTHOR(S): Agius, Lawrence M.
CORPORATE SOURCE: St. Luke's Hospital, Department of Pathology, University of Malta, Msida, Malta
SOURCE: Medical Hypotheses (2004), 62(4), 587-592
CODEN: MEHYDY; ISSN: 0306-9877
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. With strict ref. to how AIDS dementia somehow evolves from HIV infection through stages of initial monocyte-macrophage stimulation via a series of transendothelial and infiltrative events, it is perhaps significant to consider systemic body involvement by the HIV-assocd. processes to culminate in a concerted series of effects involving cascades and amplifications of action of cytokines and chemokines. Indeed, in terms that would implicate neurons only secondarily in AIDS dementia, one might perhaps consider HIV-1-dementia as an effective result of ongoing **inflammation** in the brain dependent not only on macrophage-**microglial activation** and replication, but also on glial participation in an overall process particularly conducive to increasing the brain HIV-1 load. In effect, perhaps, HIV encephalitis would constitute a system of mutually self-enhancing series of events ranging from macrophage-monocyte activation and replication on the one hand, and also HIV-1-induced cellular effects on the other that would result in progressively amplifying neuronal injury induced by cytokines and chemokines in AIDS

DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Although neurodegenerative diseases such as Alzheimer's disease are not classically considered mediated by **inflammation** or the immune system, in some instances the immune system may play an important role in the degenerative process. Furthermore, it has become clear that the immune system itself may have beneficial effects in nervous system diseases considered neurodegenerative. Immunotherapeutic approaches designed to induce a humoral immune response have recently been developed for the treatment of Alzheimer's disease. These studies have led to human trials that resulted in both beneficial and adverse effects. In animal models, it has also been shown that immunotherapy designed to induce a cellular immune response may be of benefit in central nervous system injury, although T cells may have either a beneficial or detrimental effect depending on the type of T cell response induced. These areas provide a new avenue for exploring immune system-based therapy of neurodegenerative diseases and will be discussed here with a primary focus on Alzheimer's disease. We will also discuss how these approaches affect **microglia activation**, which plays a key role in therapy of such diseases.
REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 6 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 2003:778971 HCAPLUS
DOCUMENT NUMBER: 139:306022
TITLE: Role of cytokines in neurological disorders
AUTHOR(S): Aarli, Johan A.
CORPORATE SOURCE: Department of Neurology, University of Bergen, Norway
SOURCE: Current Medicinal Chemistry (2003), 10(19), 1931-1937
CODEN: CMCHE7; ISSN: 0929-8673
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. The balance between cytokines with pro- and anti-inflammatory effects contributes to the course of the Guillain-Barre syndrome and chronic inflammatory demyelinating polyneuropathy. TNFα seems to be an important factor in the cascade of events leading to demyelination and even axonal damage. During the acute phase, the serum concns. of TNFα and IL-6 are elevated while anti-inflammatory cytokines are up-regulated in the recovery phase. Cytokines also have a key role in the pathogenesis of multiple sclerosis and most data suggest that this effect is mediated by myelin-specific CD4 T lymphocytes secreting Th type 1 cytokines. However, several different immune cells including B lymphocytes, CD8 T lymphocytes and NK T lymphocytes are also involved in the pathogenesis. Both Th1 and Th2 lymphocytes and cytokines probably participate in the development of myasthenia gravis (MG). The IFNα prodn. is probably related to the severity of the disease, with clin. improvement assocd. with decreased prodn. The serum levels of IL-18 are significantly elevated in MG, with highest concns. in patients with generalized disease. The immune system may be involved in the pathogenesis of AD by the effect of microglia, which can induce **microglial activation** with subsequent release of pro-inflammatory cytokines. In parkinsonism, there is evidence of chronic **inflammation** in the substantia nigra and striatum. Activated microglia, producing proinflammatory cytokines, surround the degenerating dopaminergic neurons and may contribute to the dopaminergic neuron loss. Studies of patients with epilepsy and animals with exptl. induced seizures indicate that

cytokines may also influence the electrophysiol. properties of neurons.
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 7 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Cited References

ACCESSION NUMBER: 2003:359389 HCAPLUS
DOCUMENT NUMBER: 138:383682
TITLE: Regulated expression of sodium-dependent glutamate transporters and synthetase: A neuroprotective role for activated microglia and macrophages in HIV infection?
AUTHOR(S): Gras, Gabriel; Chretien, Fabrice; Vallat-Decouvelaere, Anne-Valerie; Le Pavec, Gwenaelle; Porcheray, Fabrice; Bossuet, Christophe; Leone, Cathie; Mialocq, Patricia; Dereuddre-Bosquet, Nathalie; Clayette, Pascal; Le Grand, Roger; Creminon, Christophe; Dormont, Dominique; Rimaniol, Anne-Cecile; Gray, Francoise
CORPORATE SOURCE: CEA, Service de Neurovirologie, DSV/DRM, Centre de Recherches du Service de Sante des Armees, EPHE, IPSC, Fontenay aux Roses, 92265, Fr.
SOURCE: Brain Pathology (2003), 13(2), 211-222
CODEN: BRPAE7; ISSN: 1015-6305
PUBLISHER: International Society of Neuropathology
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. It is now widely accepted that neuronal damage in HIV infection results mainly from **microglial activation** and involves apoptosis, oxidative stress, and glutamate-mediated neurotoxicity. Glutamate toxicity acts via 2 distinct pathways: an excitotoxic one in which glutamate receptors are hyperactivated, and an oxidative one in which cystine uptake is inhibited, resulting in glutathione depletion and oxidative stress. A no. of studies show that astrocytes normally take up glutamate, keeping extracellular glutamate concn. low in the brain and preventing excitotoxicity. This action is inhibited in HIV infection, probably due to the effects of inflammatory mediators and viral proteins. Other in vitro studies as well as in vivo expts. in rodents following mech. stimulation, show that activated microglia and brain macrophages express high affinity glutamate transporters. These data have been confirmed in chronic **inflammation** of the brain, particularly in SIV infection, where activated microglia and brain macrophages also express glutamine synthetase. Recent studies in humans with HIV infection show that activated microglia and brain macrophages express the glutamate transporter EAAT-1 and that expression varies according to the disease stage. This suggests that, besides their recognized neurotoxic properties in HIV infection, these cells also have a neuroprotective function, and may partly make up for the inhibited astrocytic function, at least temporarily. This hypothesis might explain the discrepancy between **microglial activation** which occurs early in the disease, and neuronal apoptosis and neuronal loss which is a late event. Here, the authors discuss the possible neuro-protective and neurotrophic roles of activated microglia and macrophages that may be generated by the expression of high affinity glutamate transporters and glutamine synthetase, 2 major effectors of glial glutamate metab., and the implications for HIV-induced neuronal dysfunction, the underlying cause of HIV dementia.

REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 8 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

h eb c g cg b cg eb

Full Text | Citing References

ACCESSION NUMBER: 2003:174602 HCAPLUS
DOCUMENT NUMBER: 138:203252
TITLE: The association of **microglial activation** and amyloid reduction in APP+PS1 transgenic mice
AUTHOR(S): Morgan, Dave; Jantzen, Paul; Wilcock, Donna; DiCarlo, Giovanni; Ugen, Ken; Gordon, Marcia
CORPORATE SOURCE: Alzheimer Research Laboratory, Departments of Pharmacology and Medical Microbiology / Immunology, University of South Florida, Tampa, FL, 33612-4799, USA
SOURCE: Current Medicinal Chemistry: Immunology, Endocrine & Metabolic Agents (2003), 3(1), 27-32
CODEN: CMCIC8; ISSN: 1568-0134
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. One increasingly dominant hypothesis regarding the pathogenesis of Alzheimer dementia is the **inflammation** hypothesis. In brief, this hypothesis argues that at least some of the neurodegeneration found in this disease is secondary to excessive activation of microglia and astrocytes, resulting in secretion of pro-inflammatory mediators, activation of the complement cascade and degeneration of synapses and neurons. The APP+PS1 transgenic mouse is a model of Aβ amyloid deposition that results in a phenotype resembling some but not all aspects of Alzheimer's. The authors' group has evaluated a no. of manipulations designed to both exacerbate and ameliorate the **microglial activation** in this transgenic model, ranging from LPS injections, administration of anti-Aβ antibodies and treatment with anti-inflammatory drugs. Contrary to the authors' original predictions that **microglial activation** should exacerbate the Alzheimer phenotype in these mice, the authors find that treatments that cause **microglial activation** are assocd. with reduced amyloid loads. These data are discussed in the context of differences between the murine and human immune systems and qual. differences in the Aβ deposits found in these mouse models compared to human specimens.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 9 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:11998 HCAPLUS
DOCUMENT NUMBER: 138:202489
TITLE: Role of microglia in **inflammation**-mediated neurodegenerative diseases: Mechanisms and strategies for therapeutic intervention
AUTHOR(S): Liu, Bin; Hong, Jau-Shyong
CORPORATE SOURCE: Neuropharmacology Section, Laboratory of Pharmacology and Chemistry, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2003), 304(1), 1-7
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

h eb c g cg b cg eb

AB A review. Evidence from postmortem anal. implicates the involvement of microglia in the neurodegenerative process of several degenerative neurol. diseases, including Alzheimer's disease and Parkinson's disease. It remains to be detd., however, whether **microglial activation** plays a role in the initiation stage of disease progression or occurs merely as a response to neuronal death. Activated microglia secrete a variety of proinflammatory and neurotoxic factors that are believed to induce and/or exacerbate neurodegeneration. In this article, we summarize recent advances on the study of the role of microglia based on findings from animal and cell culture models in the pathogenesis of neurodegenerative diseases, with particular emphasis on Parkinson's disease. In addn., we also discuss novel approaches to potential therapeutic strategies.

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 10 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:611139 HCAPLUS
DOCUMENT NUMBER: 138:53334
TITLE: Amyloid β-peptide and amyloid pathology are central to the oxidative stress and inflammatory cascades under which Alzheimer's disease brain exists
AUTHOR(S): Butterfield, D. Allan; Griffin, Sue; Munch, Gerald; Pasinetti, Giulio Maria
CORPORATE SOURCE: Sanders-Brown Center on Aging, Center of Membrane Sciences, Department of Chemistry, University of Kentucky, Lexington, KY, 40506-0055, USA
SOURCE: Journal of Alzheimer's Disease (2002), 4(3), 193-201
CODEN: JADIF9; ISSN: 1387-2877
PUBLISHER: IOS Press
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Alzheimer's disease (AD) brain is characterized by excess deposition of amyloid β-peptide (Aβ), particularly the 42-amino acid peptide [Aβ(1-42)] and by extensive oxidative stress. Several sources of the oxidative stress and inflammatory cascades are likely, including that induced by advanced glycation end products, **microglial activation**, and by Aβ(1-42) and its sequelae. This review briefly examines each of these sources of oxidative stress and **inflammation** in AD brain and discusses their potential roles in the clin. progression of AD dementia.

REFERENCE COUNT: 94 THERE ARE 94 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 11 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:545971 HCAPLUS
DOCUMENT NUMBER: 137:245440
TITLE: CD40-CD40L interaction in Alzheimer's disease
AUTHOR(S): Tan, Jun; Town, Terrence; Mullan, Mike
CORPORATE SOURCE: Department of Psychiatry, The Roskamp Institute, University of South Florida, Tampa, FL, 33613, USA
SOURCE: Current Opinion in Pharmacology (2002), 2(4), 445-451
CODEN: COPUBK; ISSN: 1471-4892
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

h eb c g cg b cg eb

AB A review. Increasing evidence supports a role of the CD40 receptor-CD40 ligand (CD40-CD40L) interaction in the pathogenesis of Alzheimer's disease (AD). It has previously been shown that this dyad acts synergistically with the Alzheimer amyloid-β peptide to promote **microglial activation**. Reactive microglia produce potentially neurotoxic substances such as tumor necrosis factor α and the reactive oxygen species nitric oxide, which can induce bystander neuronal injury at high levels. When a transgenic mouse model of AD is crossed with an animal deficient in CD40L, the resulting phenotype is deficient in the gliosis obsd. in a mouse model of AD in which CD40L is present. Addnl., these crossed animals have complete absence of AD-like neuronal Tau hyperphosphorylation, a marker of the pre-neuronal tangle pathol. in AD patients. This suggests that the CD40-CD40L system is a crit. enhancer of **microglial activation** in an AD transgenic mouse model and that such activation is assocd. with an increase in a key indicator of neuronal stress. Conversely, the finding that reduced CD40-CD40L interaction is assocd. with reduced chronic microgliosis and Tau hyperphosphorylation supports the view that, in general, mechanisms that reduce microgliosis will be beneficial in AD. CD40 and CD40 ligand mediate **inflammation** in diseases such as atherosclerosis and multiple sclerosis. Tan, Town and Mullan discuss the relevance of this receptor-ligand dyad to Alzheimer's disease, particularly exploring its role in pro-inflammatory **microglial activation** and neuronal injury.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 12 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:512675 HCAPLUS
DOCUMENT NUMBER: 137:292360
TITLE: Role of nitric oxide in **inflammation**-mediated neurodegeneration
AUTHOR(S): Liu, Bin; Gao, Hui-Ming; Wang, Jiz-yuh; Jeohn, Gwang-Ho; Cooper, Cynthia L.; Hong, Jau-Shyong
CORPORATE SOURCE: Neuropharmacology Section, Laboratory of Pharmacology and Chemistry, National Institute of Environmental Health Sciences/National Institutes of Health, NC, USA
SOURCE: Annals of the New York Academy of Sciences (2002), 962(Nitric Oxide), 318-331
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Increasing evidence has suggested that **inflammation** in the brain is closely assocd. with the pathogenesis of several degenerative neurol. disorders, including Parkinson's disease, Alzheimer's diseases, multiple sclerosis, amyotrophic lateral sclerosis, and AIDS dementia. The hallmark of brain **inflammation** is the activation of glial cells, esp. that of microglia that produce a variety of proinflammatory and neurotoxic factors, including cytokines, fatty acid metabolites, free radicals-such as nitric oxide (NO) and superoxide. Excessive prodn. of NO, as a consequence of nitric oxide synthase induction in activated glia, has been attributed to participate in neurodegeneration. Using primary mixed neuron-glia cultures and glia-enriched cultures prepd. from embryonic rodent brain tissues, we have systemically studied the relationship between the prodn. of NO and neurodegeneration in response to stimulation by the inflammagen lipopolysaccharide. This review summarizes our recent findings on the kinetics of NO generation, the relative contribution of microglia and astrocytes to NO accumulation, the relationship between NO

prodn. and neurodegeneration, and points of intervention along the pathways assocd. with NO generation to achieve neuroprotection. We also describe our results relating to the effect of several opioid-related agents on **microglial activation** and neuroprotection. Among these agents, the opioid receptor antagonist naloxone, esp. its non-opioid enantiomer (+)-naloxone, promises to be of potential therapeutic value for the treatment of **inflammation**-related diseases.

REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 13 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:499452 HCAPLUS
DOCUMENT NUMBER: 138:87195
TITLE: Neuroinflammation in Alzheimer's disease: potential targets for disease-modifying drugs
AUTHOR(S): Huell, M.; Hampel, H.
CORPORATE SOURCE: Dep. Psychiatry, Univ. Freiburg, Med. School, Freiburg, 79104, Germany
SOURCE: Ernst Schering Research Foundation Workshop (2002), 39, 159-178
CODEN: ESRWEL; ISSN: 0947-6075
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Topics discussed include neuroptahol. of Alzheimer's disease; components of neuro-**inflammation** in the central nervous system; **microglial activation** in AD; cytokines, acute-phase protein and complement components; cyclooxygenase 1 and 2 and the prodn. of prostaglandins; neuroinflammation in animal models and cell cultures; and vaccination studies in animal models. The epidemiol. and clin. data on anti-inflammatory drugs and neuroinflammation and possible drug targets are underlined.

REFERENCE COUNT: 104 THERE ARE 104 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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Full Text | Citing References

ACCESSION NUMBER: 2002:490142 HCAPLUS
DOCUMENT NUMBER: 137:276617
TITLE: **Microglial activation** and inflammatory reaction preceding neurodegeneration in Sandhoff disease
AUTHOR(S): Wada, Ryuichi; Tifft, Cynthia J.; Proia, Richard L.
CORPORATE SOURCE: Department of Pathology, Hirosaki University School of Medicine, Hirosaki, Japan
SOURCE: International Congress Series (2001), 1223(New Developments in Glycomedicine), 23-27
CODEN: EXMDA4; ISSN: 0531-5131
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Sandhoff disease is a lysosomal storage disorder characterized by the absence of β-hexosaminidase and storage of GM2 ganglioside and related glycolipids in the central nervous system. The glycolipid storage causes severe neurodegeneration and progressive decline of neurol. function that leads to death at an early stage of life. The pathogenetic

mechanisms of neurodegeneration in this disease are poorly understood. In Sandhoff disease model, mice apoptotic cell death was prominent in the brainstem and spinal cord during the rapid decline of neurol. function. By global gene expression and histol. analyses, the authors identified an inflammatory reaction mediated by microglia/macrophages that precedes neuronal apoptosis. When the inflammatory response was suppressed by bone marrow transplantation, neuronal apoptosis was suppressed. We suggest that the inflammatory reaction may have a direct role in the neurodegenerative process. Thus, this lysosomal storage disease may have similarities to other neurodegenerative disorders, such as Alzheimer's, HIV dementia and prion diseases, where inflammatory processes are believed to participate directly in neuronal cell death.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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ACCESSION NUMBER: 2001:918698 HCAPLUS
DOCUMENT NUMBER: 137:31033
TITLE: Modeling **microglial activation** in Alzheimer's disease with human postmortem microglial cultures
AUTHOR(S): Lue, Lih-Fen; Walker, Douglas G.; Rogers, Joseph
CORPORATE SOURCE: L. J. Roberts Alzheimer's Center, Sun Health Research Institute, Sun City, AZ, 85351, USA
SOURCE: Neurobiology of Aging (2001), 22(6), 945-956
CODEN: NEAGDO; ISSN: 0197-4580
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Alzheimer's disease (AD) is a uniquely human disorder. Despite intense research, the lack of availability of model systems has hindered AD studies though in recent years transgenic mouse models have been produced, which develop AD-like amyloid beta peptide (Aβ) plaques. For the study of inflammatory changes in AD brains, these transgenic mice may have limitations due to differences in the innate immune system of humans and rodents. Many studies of inflammatory processes in AD have focused on the role of activated microglia. Over the last 8 yr, the authors' research has focused on the properties of human microglia cultured from brain tissues of AD and non-demented (ND) individuals. As these are the cells obsd. to be activated in AD tissues, they represent a useful system for modeling the inflammatory components of AD. In this review, the authors summarize data by their group and others on the use of microglia for AD-related inflammatory research, with emphasis on results using human postmortem brain microglia. A range of products have been shown to be produced by human postmortem microglia, both constitutively and in response to treatment with Aβ, including proinflammatory cytokines such as interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF) α, and macrophage colony stimulating factor (M-CSF), along with complement proteins, esp. C1q, superoxide radicals and neurotoxic factors. In their studies, the authors have demonstrated that there was a significant difference between AD and ND microglia in terms of their secretion of M-CSF and C1q. The authors also discuss the role of putative Aβ microglial receptors, particular recent data showing a role for the receptor for advanced glycation end-products (RAGE) in mediating the responses of human microglia to Aβ. Finally, the authors' studies on the use of an Aβ spot paradigm to model microglia interactions with plaques demonstrated that many of the features of AD **inflammation** can be modeled with postmortem brain derived microglia.

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REFERENCE COUNT: 123 THERE ARE 123 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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ACCESSION NUMBER: 2001:708591 HCAPLUS
DOCUMENT NUMBER: 136:116885
TITLE: Immunological aspects of microglia: relevance to Alzheimer's disease
AUTHOR(S): Benveniste, E. N.; Nguyen, V. T.; O'Keefe, G. M.
CORPORATE SOURCE: Department of Cell Biology, The University of Alabama at Birmingham, Birmingham, AL, 35294-0005, USA
SOURCE: Neurochemistry International (2001), 39(5-6), 381-391
CODEN: NEUIDS; ISSN: 0197-0186
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Alzheimer's disease (AD) is a progressive dementing neurol. illness, and the most frequent cause of dementia in the elderly. Neuritic plaques are one of the main neuropathol. findings in AD, and the major protein component is the β-amyloid protein (Aβ). Another striking feature of neuritic plaques is the presence of activated microglia, cytokines, and complement components, suggestive of "inflammatory foci" within AD brain. In this review, the authors will examine the mechanisms by which microglia become activated in AD, emphasizing the role in the Aβ protein and proinflammatory cytokines. As well, pathways for suppression of **microglial activation** by immunosuppressive cytokines will be described. **Inflammation** mediated by activated microglia is an important component of AD pathophysiol., and strategies to control this response could provide new therapeutic approaches for the treatment of AD.

REFERENCE COUNT: 109 THERE ARE 109 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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ACCESSION NUMBER: 2001:708590 HCAPLUS
DOCUMENT NUMBER: 136:116884
TITLE: CD40 signaling and Alzheimer's disease pathogenesis
AUTHOR(S): Town, T.; Tan, J.; Mullan, M.
CORPORATE SOURCE: Roskamp Institute, Department of Psychiatry, University of South Florida, Tampa, FL, 33613, USA
SOURCE: Neurochemistry International (2001), 39(5-6), 371-380
CODEN: NEUIDS; ISSN: 0197-0186
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review discussed CD40 signaling and Alzheimer's disease pathogenesis. The interaction between CD40 and its cognate ligand, CD40 ligand, is a primary regulator of the peripheral immune response, including modulation of T lymphocyte activation, B lymphocyte differentiation and antibody secretion, and innate immune cell activation, maturation, and survival. Recently, we and others have identified CD40 expression on a variety of CNS cells, including endothelial cells, smooth muscle cells, astroglia and microglia, and have found that, on many of these cells, CD40 expression is enhanced by pro-inflammatory stimuli. Importantly, the CD40-CD40 ligand

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interaction on microglia triggers a series of intracellular signaling events that are discussed, beginning with Src-family kinase activation and culminating in **microglial activation** as evidenced by tumor necrosis factor-α secretion. Based on the involvement of **microglial activation** and brain **inflammation** in Alzheimer's disease pathogenesis, we have investigated co-stimulation of microglia, smooth muscle, and endothelial cells with CD40 ligand in the presence of low doses of freshly solubilized amyloid-β peptides. Data reviewed herein show that CD40 ligand and amyloid-β act synergistically to promote pro-inflammatory responses by these cells, including secretion of interleukin-1β by endothelial cells and tumor necrosis factor-α by microglia. As these cytokines have been implicated in neuronal injury, a comprehensive model of pro-inflammatory CD40 ligand and amyloid-β initiated Alzheimer's disease pathogenesis (mediated by multiple CNS cells) is proposed.

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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ACCESSION NUMBER: 2001:606321 HCAPLUS
DOCUMENT NUMBER: 136:303352
TITLE: Celastrol, a potent antioxidant and anti-inflammatory drug, as a possible treatment for Alzheimer's disease
AUTHOR(S): Allison, Anthony C.; Cacabelos, Ramon; Lombardi, Valter R. M.; Alvarez, Xoan A.; Vigo, Carmen
CORPORATE SOURCE: SurroMed Corporation, Palo Alto, CA, USA
SOURCE: Progress in Neuro-Psychopharmacology & Biological Psychiatry (2001), 25(7), 1341-1357
CODEN: PNPPD7; ISSN: 0278-5846
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. In the brains of patients with Alzheimer's disease (AD) signs of neuronal degeneration are accompanied by markers of **microglial activation**, **inflammation**, and oxidant damage. The presence of nitrotyrosine in the cell bodies of neurons in AD suggests that peroxynitrite contributes to the pathogenesis of the disease. A drug with antioxidant and anti-inflammatory activity may prevent neuronal degeneration in AD. Celastrol, a plant-derived triterpene, has these effects. In low nanomolar concns. celastrol was found to suppress the prodn. by human monocytes and macrophages of the pro-inflammatory cytokines TNF-α and IL-1β. Celastrol also decreased the induced expression of class II MHC mols. by microglia. In macrophage lineage cells and endothelial cells celastrol decreased induced but not constitutive NO prodn. Celastrol suppressed adjuvant arthritis in the rat, demonstrating in vivo anti-inflammatory activity. Low doses of celastrol administered to rats significantly improved their performance in memory, learning and psychomotor activity tests. The potent antioxidant and anti-inflammatory activities of celastrol, and its effects on cognitive functions, suggest that the drug may be useful to treat neurodegenerative diseases accompanied by **inflammation**, such as AD.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 19 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

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ACCESSION NUMBER: 2001:462082 HCAPLUS
DOCUMENT NUMBER: 136:149146
TITLE: Crosstalk between components of the blood brain barrier and cells of the CNS in **microglial activation** in AIDS
AUTHOR(S): Langford, Dianne; Masliah, Eliezer
CORPORATE SOURCE: Departments of Neurosciences, University of California San Diego, La Jolla, CA, 92093, USA
SOURCE: Brain Pathology (2001), 11(3), 306-312
CODEN: BRPAE7; ISSN: 1015-6305
PUBLISHER: International Society of Neuropathology
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. During the progression of AIDS, a majority of patients develop cognitive disorders such as HIV encephalitis (HIVE) and AIDS dementia complex (ADC), which correlate closely with macrophage infiltration into the brain and **microglial activation**. **Microglial activation** occurs in response to infection, **inflammation** and neurol. disorders including HIVE, Alzheimer's disease, Parkinson's disease and multiple sclerosis. Microglia can be activated by immunoreactive cells independent of, but enhanced by HIV infection, from at least two routes. Activation may occur from signals originating from activated monocytes and lymphocytes in the blood stream, which initiate a cascade of stimuli that ultimately reach microglia in the brain or from activated macrophages/microglia/astrocytes within the brain. Effects of **microglial activation** stemming from both systemic and CNS HIV infection act together to commence signaling feedback, leading to HIVE and increased neurodegeneration. Most recent data indicate that in AIDS patients, **microglial activation** in the brain with subsequent release of excitotoxins, cytokines and chemokines leads to neurodegeneration and cognitive impairment. Since the presence of HIV in the brain results from migration of infected monocytes and lymphocytes across the vascular boundary, the development of novel therapies aimed at protecting the integrity of the blood brain barrier (BBB) upon systemic HIV infection is crit. for controlling CNS infection.

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 20 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Cited References

ACCESSION NUMBER: 1999:243819 HCAPLUS
DOCUMENT NUMBER: 131:42723
TITLE: HIV-1-induced neuronal injury in the developing brain
AUTHOR(S): Epstein, Leon G.; Gelbard, Harris A.
CORPORATE SOURCE: Departments of Neurology, Pediatrics, Microbiology and Immunology, University of Rochester, NY, USA
SOURCE: Journal of Leukocyte Biology (1999), 65(4), 453-457
CODEN: JLBIE7; ISSN: 0741-5400
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 63 refs. HIV-1 infection of the nervous system causes neuronal injury and death, resulting in cognitive, motor, and behavioral dysfunction in both adults and children. In infants a characteristic feature of HIV-1 infection is impaired brain growth resulting in secondary microcephaly with onset between 2 and 4 mo of age. This post-natal period of brain development is particularly vulnerable to excitotoxic neuronal injury due to the active synaptogenesis and pruning that takes place at this age assocd. with over-expression of excitatory amino acid (EAA)

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receptors. HIV-1 infection of brain microglia and perivascular macrophages results in chronic **inflammation** manifest pathol. as diffuse **microglial activation** and reactive astrogliosis. Several inflammatory products of activated microglia, including tumor necrosis factor α (TNF-α) and platelet-activating factor (PAF) have been shown to act as neuronal toxins. This toxic effect can be antagonized by blocking NMDA (or AMPA) glutamate receptors, suggesting that (weak) excitotoxicity leads to oxidative stress, neuronal injury, and apoptosis. HIV-1 infection and chronic **inflammation** may also contribute disruption of the blood-brain barrier and could result in further entry into the CNS of toxic viral or cellular products or addnl. HIV-1-infected cells. We hypothesize that prolonged **microglial activation** during HIV-1 infection underlies the neuronal injury and impaired brain growth in affected infants. Further investigation of the interaction between HIV-1-infected/activated microglia and developing neurons seems warranted. The current understanding of HIV neuropathogenesis implies that therapeutic strategies should target the sustained immune activation in microglia, attempt to repair the integrity of the blood-brain barrier, and provide "neuroprotection" from excitotoxic neuronal injury.

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 21 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN

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ACCESSION NUMBER: 1996:394714 HCAPLUS
DOCUMENT NUMBER: 125:83112
TITLE: Molecular mechanisms of **microglial activation**. A. Implications for regeneration and neurodegenerative diseases
AUTHOR(S): Gebicke-Haerter, P. J.; Van Calker, D.; Noerenberg, W.; Illes, P.
CORPORATE SOURCE: Dep. of Psychiatry, Univ. of Freiburg, Freiburg, D-79104, Germany
SOURCE: Neurochemistry International (1996), 29(1), 1-12
CODEN: NEUIDS; ISSN: 0197-0186
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review, with 165 refs. Microglial are the resident immunocompetent cells of the brain, comparable to other tissue macrophages, e.g. Kupffer cells in the liver or Langerhans cells in the skin. In disease, however, the central nervous system appears to be a largely immunosuppressive environment, which previously led to the hypothesis that it is an "immunol. privileged" organ. Nevertheless, microglia can be activated by various internal and external stimuli, resulting in expression of cytokines and other mediators of **inflammation**. The mol. mechanisms converting those signals into specific microglial responses are a field of intensive research efforts. These have been performed both on cultured microglia and in vivo. Although the situation in vivo is sometimes difficult to interpret, considerable progress on the mol. level has been made using a no. of excellent animal model systems combined with advanced detection techniques. Moreover, isolation and culture of microglia is becoming a std. method in an increasing no. of labs., which allows a closer look at their reactions towards a variety of test substances. Both aspects have been covered in this paper. It turns out that microglia are extremely sensitive towards any kind of stimulus. They are probably the first cells in the brain "sensing" changes in the periphery, and the summarized data suggest that microglia may even react in a specific manner in response to a specific stimulus. Under the notion that not only

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multiple sclerosis, but also further chronic degenerative diseases of the brain, are based on a common autoimmune mechanism, better insights into **microglial activation** and is prolonged maintenance are of outstanding scientific interest.

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